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EXAMINER	
JOIKE, MICHELE K	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,219	SCHARER-BRODBECK, CLAUDIA	
	Examiner	Art Unit	
	MICHELE K. JOIKE	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-30* is/are pending in the application.

4a) Of the above claim(s) *19-21, 29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/6/05, 6/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on July 24, 2008 is acknowledged.

Claims 1-17 and 22-28 are examined.

Specification

The disclosure is objected to because of the following informalities: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers. These sequences include the sequences listed in the claims and throughout the specification. Nucleotide sequences with 10 or more nucleotides and amino acid sequences with 4 or more amino acids require sequence identifiers. If the Sequence Listing required for the instant application is identical to that of another application, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP § 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP § 2422.02).

In paragraph 19 (and wherever else it appears in the specification), the signal peptide KLGT needs a sequence identifier if the KLGT is an amino acid sequence.

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 22-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "suitable" in claim 1 is a relative term which renders the claim indefinite. The term "suitable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat.

App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 2 and 15 recites the broad recitation at least one protein region, and the claim also recites "more preferably a full length protein" which is the narrower statement of the range/limitation. Using the term "preferably" cause confusion about the intended scope of the claim.

In claims 6, 7, 14 and 24, a "unique recognition site" is claimed. It is unclear what makes the recognition site unique. Do applicants mean an introduced recognition site, or one that is already present but has one or more characteristics that make it different than other recognition sites?

Claim 8 recites the limitation "said second DNA sequence" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. It is unclear if the second sequence it suppose to be the donor sequence or the second target sequence, as there is no "second DNA sequence".

Claim 9 is confusing because the claim states that the first DNA sequence of the target vector replaces at least one CDR region of the antibody, however, it appears from claim 1 that the toxin is to be replaced. Since it is unclear from claim 8 where the

antibody is present, this also makes this claim and claims 10, 25 and 26 confusing, as well.

Claim 11 recites the limitation "the signal peptide" in line2. There is insufficient antecedent basis for this limitation in the claim. Is the signal peptide added to the construct or is it endogenous to the toxin?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13-16, 22-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a yeast cell, does not reasonably provide enablement for any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is a method for constructing randomized gene libraries in cells by introducing into the cells a target vector containing

the *K. lactis* gamma toxin, and a donor sequence used to replace the gamma toxin through homologous recombination.

Breadth of the claims: The method is broad because any cell can be used from any organism can be used.

Guidance of the specification: The specification only discloses use of yeast cells in its examples. Although the specification mentions that other cells can be used, it does not mention any cells specifically, nor describes how they would function in the method.

Predictability and state of the art: The art is silent on using a gamma toxin in any cells other than in microbial cells. Using this method with the gamma toxin is unpredictable, because the gamma toxin has not been used in mammalian cells, for example. The claims encompass every known organism, and it is unclear how this method would function in the different cells.

Amount of experimentation necessary: Again, since it is unknown what effect the gamma toxin would have on cells other than yeast, the amount of experimentation to test this method with other organisms is undue. There is no guidance as to what cells are suitable for this method. The method would have to be optimized to the organism since the method also needs to be performed under suitable conditions.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to use this method in any cell.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12-17, 24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meinhardt et al in view of Butler et al, and in further view of US 6,410,271.

Meinhardt et al (IDS ref. C1, especially pp. 318, 319, 322, Figures 1 and 2) teach the plasmid pGLK1, which contains the *K. lactis* killer toxin. Another plasmid contains an *aph* gene, encoding an aminoglycoside phosphotransferase under the UCS5 promoter. The plasmid also contains a LEU2 marker. The gene and promoter are flanked by sequences derived from the ORF2 that encodes the killer toxin for integration of the LEU2 and UCS5/*aph* into the ORF2 by homologous recombination. ORF2 encodes the α and β subunits of the killer toxin. Integration of the LEU2 and *aph* genes disrupts the ORF2. The resulting plasmids are linearized with restriction endonucleases, and then transformed into *K. lactis*. However, they do not teach use of the gamma toxin or construction of a library.

Butler et al (Yeast 7: 617-625, 1991, especially p. 617) teach plasmid pGLK1 carrying the gamma subunit gene expressed from a GAL7 promoter transformed into *S. cerevisiae* cells. The plasmid is linear. However, they do not teach construction of a

library. *S. cerevisiae* is usually grown at 30°C, as evidenced by Sherman (Methods Enzymol. 350:2-41, 2002, see p. 11).

US 6,410,271 (especially columns 14 and 25-27) teaches a methods for generating highly diverse libraries of expression vectors encoding fusion proteins, such as single-chain antibodies, via homologous recombination in yeast. The method comprises transforming into yeast cells a linearized yeast expression vector; and having homologous recombination occur between the vector and the insert sequence such that the insert sequence is included in the vector in the transformed yeast cells. Gene shuffling can be used to randomize the library.

The ordinary skilled artisan, desiring to construct randomized gene libraries by introducing into cells a target vector with a gamma toxin and a donor sequence, which homologously recombine, would have been motivated to combine the teachings of Meinhardt et al teaching the plasmid pGLK1, which contains the *K. lactis* killer toxin recombining with the *aph* gene with the teachings of Butler et al teaching the plasmid pGLK1 carrying the gamma subunit gene, with the teachings of US 6,410,271 teaching a methods for generating highly diverse libraries of expression vectors encoding fusion proteins, such as single-chain antibodies, via homologous recombination in yeast because Meinhardt et al state that the killer toxin is useful for killing other strains not carrying the plasmid and can be stably maintained in other yeasts, and Butler et al state that the gamma subunit of the toxin alone is required for inhibition. Furthermore, US 6,410,271 teaches that homologous recombination occurs between DNA sequences at the two homologous recombination sites, and a reciprocal exchange of the DNA content

occurs, and a library can be created using different sequences. By using homologous recombination in yeast, genes can be cloned into a plasmid vector without a ligation step. It would have been obvious to one of ordinary skill in the art to use the gamma toxin because Butler et al teach that the gamma toxin alone does not result in reduced viability and is fully reversible. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meinhardt et al, Butler et al and US 6,410,271 as applied to claims 1-7, 12-16, 24 and 27 above, and further in view of Monschau et al.

Meinhardt et al teach all of the limitations as described, however, they do not teach use of a constitutive promoter or the use of the TEF promoter from *A. gossypii*.

Butler et al teach all of the limitations as described, however, they do not teach use of a constitutive promoter or the use of the TEF promoter from *A. gossypii*.

US 6,410,271 teach all of the limitations as described, however, they do not teach use of a constitutive promoter or the use of the TEF promoter from *A. gossypii*.

Monschau et al (Applied and Envtl. Microbiol. 64(11): 4283-90, 1998, especially p. 4238) teach the use of the constitutive TEF promoter from *A. gossypii*.

The ordinary skilled artisan, desiring to use the TEF promoter, would have been motivated to combine the teachings of Meinhardt et al teaching the plasmid pGLK1,

which contains the *K. lactis* killer toxin recombining with the *aph* gene with the teachings of Butler et al teaching the plasmid pGLK1 carrying the gamma subunit gene, with the teachings of US 6,410,271 teaching a methods for generating highly diverse libraries of expression vectors encoding fusion proteins, such as single-chain antibodies, via homologous recombination in yeast, with the teachings of Monschau et al teaching the use of the TEF promoter because Monschau et al state that use of the TEF promoter leads to strong enhancement of expression. It would have been obvious to one of ordinary skill in the art to use the TEF promoter because Monschau et al teach that the promoter has constitutive expression. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meinhardt et al, Butler et al and US 6,410,271 as applied to claims 1-7, 12-16, 24 and 27 above, and further in view of Soderlind et al.

Meinhardt et al teach all of the limitations as described, however, they do not teach the donor sequence comprising a DNA sequence encoding a CDR region of an antibody.

Butler et al teach all of the limitations as described, however, they do not teach the donor sequence comprising a DNA sequence encoding a CDR region of an antibody.

US 6,410,271 teach all of the limitations as described, however, they do not teach the donor sequence comprising a DNA sequence encoding a CDR region of an antibody.

Jirholt et al (Gene 215: 471-476, 1998, especially p) teach a library containing CDRs.

The ordinary skilled artisan, desiring to use CDRs, would have been motivated to combine the teachings of Meinhardt et al teaching the plasmid pGLK1, which contains the *K. lactis* killer toxin recombining with the *aph* gene with the teachings of Butler et al teaching the plasmid pGLK1 carrying the gamma subunit gene, with the teachings of US 6,410,271 teaching a methods for generating highly diverse libraries of expression vectors encoding fusion proteins, such as single-chain antibodies, via homologous recombination in yeast, with the teachings of Jirholt et al teaching libraries containing CDRs because Jirholt et al state that combinatorial biology provides an efficient way of creating large molecular libraries, in particular to antibody genes. It would have been obvious to one of ordinary skill in the art to use CDRs because Jirholt et al teach that shuffling CDRs allows for greater variability in the library. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE K. JOIKE whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

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